REMARKS

Claims 23, 24, and 26-28 are pending in the present application.

At the outset, Applicants wish to thank Examiner Zucker for the indication that Claim 24 is allowed (paper number 13, page 9, numbered paragraphs 13 and 14). Reconsideration of the remaining claims (Claims 23 and 26-28) is requested in view of the following.

Present Claims 23 and 26 relate to crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester produced by:

(1) subjecting N-L-α-aspartyl-L-phenylalanine 1-methyl ester and 3-(3-methoxy-4-hydroxyphenyl)propionaldehyde or a derivative thereof to reductive alkylation in a solvent to obtain N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester; and

(2) crystallizing said N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester,

wherein said reductive alkylation comprises catalytic hydrogenation, and

wherein said derivative thereof is selected from the group consisting of

3-(3-methoxy-4-hydroxyphenyl)-2-propenylaldehyde,

3-(3-methoxy-4-protected-hydroxyphenyl)propionaldehyde,

3-(3-methoxy-4-protected-hydroxyphenyl)-2-propenylaldehyde, and

acetals derived therefrom.

Present Claims 27 and 28 relate to certain sweetening agents which contain such crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester.

The cited references contain no disclosure or suggestion of such a crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester. Moreover, these references contain no teaching that would instill a reasonable expectation of success for the presently claimed methods into one of skill in the art. Accordingly, these references cannot affect the patentability of the present claims.

The rejections of: (a) Claims 23 and 26 under 35 U.S.C. § 103(a) over U.S. Patent No. 5,480,668 (Nofre et al) in view of U.S. Patent No. 5,510,508 (Claude et al); and (b) Claims 27 and 28 under 35 U.S.C. § 103(a) over U.S. Patent No. 5,480,668 (Nofre et al) in view of U.S. Patent No. 5,510,508 (Claude et al), are respectfully traversed.

At column 7, lines 48-51 of Nofre et al, there is found a description showing that the 3,3-dimethylbutyl derivative of aspartame has been crystallized in the solvent of ethanol/water or acetonitrile. However, contrary to the assertion by the Examiner, this reference does not describe that the series of the compounds appearing in Table 1 can be purified with the same or similar crystallization method and/or with the same solvent. Further, with respect to the compound 18 shown in the Table 1 of Nofre et al, this reference does not describe even the following:

(1) How the compound has been purified (how to purify);

(2) Whether or not the compound can be isolated in the crystalline form; or

(3) Even if the compound exists as a crystalline form.

As conceded by the Examiner, Nofre et al is also deficient in that this reference fails to disclose a synthetic method using catalytic hydrogenation. Instead, Nofre et al disclose a reductive alkylation process for the synthesis of N-[N-[3-(3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester by employing sodium cyanoborohydride.

Claude et al is cited by the Examiner as disclosing a reduction alkylation reaction between 3,3-dimethylbutyraldehyde and aspartame in a methanol solution in the presence of a platinum catalyst and hydrogen gas at 1 bar at room temperature (column 3, line 63 to column 4, line 26). Applicants agree that this disclosure may be found in Example 1 of Claude et al; however, when these disclosures of Nofre et al and Claude et al are combined, at best, it may support a *prima facie* case of obviousness for a method of making N-[N-[3-(3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester by reductive alkylation, but this is not the compound that is being made in the present invention.

In fact, even the combined disclosures of Nofre et al and Claude et al fail to disclose or suggest the following regarding the claimed N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester:

(1) How the compound has been purified (how to purify);

(2) Whether or not the compound can be isolated in the crystalline form; or

(3) Even if the compound exists as a crystalline form.

MPEP §2142 states: "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation... to modify the reference... Second, there must be a reasonable expectation of success. Finally, the prior art reference... must teach or suggest all the claim limitations." In the present case, since there is no disclosure of (a) crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester, (b) how to purify N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester, or (c) whether N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester even exists in the crystalline state in Nofre et al or Claude et al (individually or in combination) these references cannot support a *prima facie* case of obviousness.

The Examiner chooses to disregard these deficiencies in the disclosures of Nofre et al or Claude et al and points to the broad sweeping assertion in Nofre et al at column 7, lines 61-65 that the "other compounds according to the invention [are] obtained from aspartame by an experimental protocol similar to that described above, which will be readily accessible to those skilled in the art." Apparently, the skilled artisan is to embrace this directive by Nofre et al as pseudo-divine insight to fill in all the gaps in the disclosure of Nofre et al (see above) that are also notably absent in the disclosure of Claude et al.

Again, Applicants direct the Examiner's attention to MPEP §2142. The only disclosure or suggestion in Nofre et al or Claude et al to modify their disclosures is in regard to the replacement of reductive alkylation between 3,3-dimethylbutyraldehyde and aspartame in a methanol solution in the presence of a platinum catalyst (Claude et al) for reductive alkylation using sodium cyanoborohydride (Nofre et al) to provide an equivalent synthesis of N-[N-[3-(3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester. There is no further disclosure or suggestion in these references that would lead the artisan to readily envision that this same modification could be employed for any other compound in Table 1 of Nofre et al. Moreover, even if the artisan would have been motivated to so act, all the claim limitations for N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester have not been disclosed or suggested (*i.e.*, a crystalline form of the same).

Furthermore, the Examiner's attention is directed to paragraphs 16-20 of the Declaration of Professor Jerry Atwood ("Atwood Declaration") submitted on September 25, 2003 (a copy of which is **enclosed herewith**), which clearly and succinctly summarizes the disclosure of Nofre et al and its relationship to the claimed invention as would understood by the skilled artisan. For the Examiner's convenience, the salient features of this summary by

Professor Atwood are provided below as they relate to Nofre et al and serve to provide a summary of how one of skill in the art would interpret the disclosure of Nofre et al.

The present specification discloses the crystallization of the Aspartame derivative N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester. A detailed description of the conditions of crystallization is given. The resulting crystals are defined in terms of their X-ray powder diffraction (XRPD) pattern. As opined by Professor Atwood, "upon reading the Application, one of ordinary skill in the art would understand how to crystallize N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester, and would further know that the desired crystalline compound had been prepared by performing a standard XRPD study." (paragraph 16 of the Atwood Declaration)

With respect to the disclosure of Nofre et al, citing column 7, lines 47-51, Professor Atwood further opines: "At best, the Nofre '668 Patent teaches a general synthetic method for the production of the compounds appearing in Table 1. In fact, the only synthetic method exemplified in the Nofre '668 Patent is for N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester... Therefore, not only does the Nofre '668 Patent fail to disclose an actual synthetic method for the N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester compound, it also falls short of the mark with regard to crystallization." (paragraph 17 of the Atwood Declaration)

Applicants direct the Examiner's attention to paragraph 20 of the Atwood Declaration in which Professor Atwood summarizes the differences between the present invention and the disclosure of Nofre et al. In particular, Professor Atwood summarizes the deficiencies in the disclosure of Nofre et al and why this disclosure does not anticipate and/or render obvious the present invention. For the Examiner's convenience, paragraph 20 of the Atwood Declaration is reproduced below:

> In summary, the teachings of the Nofre '668 Patent at best provides a synthetic method for the production of the N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester molecule, but the crystallization teaching is lacking. Nofre does not teach any crystal form of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester. Therefore, based on the teaching of the Nofre '668 Patent, one of ordinary skill in the art would not find crystallization and the crystal form of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester to be obvious. It is only the Application that teaches crystallization and the crystal form of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester.

In view of the foregoing, Applicants submit that the disclosure of Nofre et al ***is*** silent with respect to any production method or crystalline form of the claimed N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester. Furthermore, Claude et al fails to compensate for these notable deficiencies. Accordingly, Nofre et al, even in combination with Claude et al, cannot affect the patentability of Claims 23 and 26.

As explained above Claim 23 is unobvious over Nofre et al and Claude et al. Claims 27 and 28 recite the presence of the crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester of Claim 23. Thus, Claims 27 and 28 are also patentable over unobvious over Nofre et al and Claude et al for at least the same reasons that Claim 23 is patentable over this reference.

For the foregoing reasons, Nofre et al and Claude et al fail to render obvious the present invention. As such, these grounds of rejection should be withdrawn.

Applicants submit that the present application is now in condition for allowance.

Early notification of such action is earnestly solicited.

Respectfully submitted,

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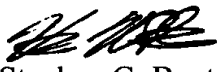

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